REMARKS

Claims 32-35 and 45-52 are pending and rejected.

Claim 45 is corrected to reflect status as PREVIOUSLY PRESENTED because it encompasses the elected specie. Claims 46-52 are withdrawn as non-elected.

Claims 53-57 are added.

Applicants respectfully request reconsideration for the following reasons.

DOUBLE PATENTING REJECTION

Claims 32-35 are rejected for nonstatutory obviousness-type double patenting over claims 1, 3, 6-9, 11, 14-16, 24, and 26-29 of Rajagopalan U.S. Patent No. 6,423,547.

Applicants respectfully disagree, at least because these claims in the '547 patent do not recite the combining and administering steps, as subsequently analyzed.

The Specification, at p. 22, teaches:

> This invention is also related to the method of preventing fluorescence quenching. It is known that cyanine dyes generally form aggregates in aqueous media, leading to fluorescence quenching. Where the presence of a hydrophobic core in the dyes leads to fluorescence quenching, the addition of a biocompatible organic solvent, such as 1-50% dimethylsulfoxide (DMSO) for example, restored fluorescence by preventing aggregation and allowed *in vivo* organ visualization. Large fluorescence enhancement of dyes have been observed under the condition where the dye is encapsulated in, i.e. forms an inclusion complex with, cyclodextrins (W.R. Bergmark et al., Dramatic fluorescence effects for coumarin laser dyes coincluded with organic solvents in cyclodextrins. *J. Phys. Chem.*, 1990, 94, 5020[[8]]-5022). However, in vivo fluorescence enhancement of dyes coinjected with biocompatible organic solvents has not been previously described. Suitable organic solvent include, but are not limited to dimethylsulfoxide (DMSO), ethyl alcohol, isopropyl alcohol, glycerol, and other biocompatible polyols such as sorbitol, mannitol, xylitol, lactitol, erythritol, polydextrose, sucrose, fructose, maltose, hydrogenated starch hydrolysate (HSH), isomalt (palitinit), polyglycerol, hyperbranched polyglycerol, acetylated polyols, maltodextrine, cyclodextrine, dianhydosorbitol, starches, polysaccharides, etc. as known to one skilled in the art.

Applicants thus teach that cyanine dyes aggregate due to the presence of a hydrophobic core. Larger dye molecules would necessarily have a larger hydrophobic core. Thus, the larger the dye molecule, the greater degree of aggregation would be expected. The greater degree of aggregation would result in greater fluorescence quenching.

Applicants teach that, under these conditions, the presence of an organic solvent would prevent the dye molecules from aggregating, and thus would prevent quenching. However, the organic solvent must be present in a defined concentration; the claims recite the organic solvent ranging from 1% to 50% of the composition.

Applicants teach that when the dye is encapsulated in cyclodextrin, there is a large fluorescence enhancement. Applicants teach, however, that "in vivo fluorescence enhancement of dyes coinjected with biocompatible organic solvents has not been previously described".

The claims recite, with emphasis added:

> A method to enhance fluorescence of at least one of a cyanine or indocyanine dye administrable to a patient for a photodiagnostic or phototherapeutic procedure, the method comprising:
>
> combining the at least one cyanine or indocyanine dye and a biocompatible organic solvent at a concentration ranging from about 1% to about 50% solvent to result in a composition that is administered to a patient after the combining, wherein the fluorescence of the composition is enhanced over the fluorescence of the cyanine or indocyanine dye itself.

Thus, Applicants claim a method where the cyanine or indocyanine dye and a biocompatible organic solvent are combined to result in a composition. The composition is administered to a patient. The in vivo fluorescence of the composition is enhanced over the fluorescence of the cyanine or indocyanine dye itself.

At least because the claims in the '547 patent lack the claimed outcome of enhanced fluorescence of the composition over the fluorescence of the dye itself, Applicants respectfully request the Double Patenting Rejection be withdrawn.

CLAIM REJECTIONS UNDER 35 U.S.C. §103

Claims 32-35 are rejected under 35 U.S.C. §103(a) as obvious over Licha U.S. Patent No. 6,083,485.

Applicants respectfully disagree, and incorporate their above analysis with respect to the claimed method, and their previous distinctions over Licha.

The standard to assess obviousness is a person of ordinary skill in the art; what would this person be taught or what could this person predict based on Licha?

The Examiner states

> First, according to the abstract of Licha et al, it is disclosed that the dyes and their biomolecule adducts may be use [*sic*] as contrast media for fluorescence and transilumination [*sic*] diagnostics in the near infrared radiation range. Thus, a skilled artisan would be motivated to use the compounds/compositions of Licha et al for fluorescence purposes.

The Examiner's conclusion is incorrect; the skilled artisan would not be motivated to use the compounds/compositions of Licha in Applicants' method to enhance fluorescence of any cyanine or indocyanine dyes.

The skilled person reading Licha would have a different purpose than Applicants' purpose.

Licha teaches dyes that overcome prior art problems of toxicity, water solubility, chemical, photophysical, and metabolic stability (Licha col. 3 lines 36-44). Licha teaches adding a hydrophilic group that improves water solubility, the water soluble group having n-octanol-water distribution coefficient of the compound ≤ 2 for 1 = 0 in the formula $B_1-(F\text{-}W_n)_m$ (Licha col. 4 lines 9-27).

Applicants, in contrast, claim a method to enhance fluorescence of cyanine or indocyanine dyes. Applicants form a composition of dye and biocompatible organic solvent, then administer the composition to a patient, and the fluorescence of the composition is enhanced over the fluorescence of the cyanine or indocyanine dye alone.

Thus, the methods are different: Licha's method seeks to overcome toxicity, water insolubility, and stability; Applicants' method enhances fluorescence of cyanine or indocyanine dyes administered dyes administered to a patient.

To the skilled person reading Licha and seeking to enhance fluorescence, Licha would teach away from Applicants' claimed method. Quoting from Applicants' September 9, 2009 Remarks (emphasis in original):

> As one example of Licha's teaching away, Licha teaches the use of cyanine dyes as already solving the problem of insufficient fluorescence. As another example of Licha's teaching away, Licha teaches that fluorescence may not be desirable. For example, Licha states
>
> > The compounds used for the method according to the invention ..., where fluorescence is desirable, have a fluorescence quantum efficiency greater than 5%, are sufficiently water-soluble, tolerable and stable in vitro and in vivo as well as photostable. They are discharged as completely as possible in as short a time as possible. (col. 8 lines 31-38, emphasis)
> >
> > and
> >
> > Surprisingly, a fluoroscopic image of a mouse (Swiss nude) taken after applying a cyanine dye using a CCD camera showed a 1000 times greater fluorescent intensity as compared to a similarly dosed porphyrin. (col. 9 lines 25-28)
>
> Based on these teachings of Licha, as well as Licha's teaching of enhanced stability and solubility, a person of ordinary skill in the art would not seek to further enhance fluorescence. Based on Licha, a person of ordinary skill in the art would be taught that cyanine alone already provides enhanced fluorescence.

Thus, the problem addressed is different. Licha's method does not address enhanced fluorescence as a need because the cyanine dye itself already addressed this need; Applicants' method does address enhanced fluorescence as a need.

To the skilled person reading Licha seeking to enhance fluorescence, Licha teaches only that the dyes "...have a fluorescence quantum efficiency greater than 5%, are sufficiently water soluble, tolerable and stable..." (col. 8 lines 34-37). Licha does not teach a person skilled in the art to combine a dye and biocompatible organic solvent to form a composition and to administer the composition to a patient to result in enhanced fluorescence of the composition over the fluorescence of the cyanine or indocyanine dye itself.

The Examiner states

> Secondly, a skilled artisan would recognize that a composition is inseparable from its properties. As a result, the properties associated with Applicant

> combining a cyanine dye and cyclodextrin would be the same as that obtain [*sic*] from Licha et al combining their cyanine and cyclodextrin. Thus, while Licha et al disclose that the addition of cyclodextrin is added for a reason different than that of Applicant, the skilled artisan would recognize that the prior art and the instant invention disclose overlapping subject matter since the same components are added to the composition. Furthermore, in response to Applicant's argument that the use of cyclodextrin, in the instant invention, is to enhance fluorescence, the fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.

Applicants respectfully disagree. The skilled artisan would not "recognize that the prior art and the instant invention disclose overlapping subject matter", at least because the skilled person reading Licha would not get any teaching that cyclodextrin can be used as one example of a biocompatible organic solvent, at a concentration ranging from about 1% to about 50%, to enhance fluorescence of the cyanine or indocyanine dye.

Applicants note their election of the specie of DMSO as the biocompatible organic solvent.

Nonetheless, cyclodextrin, as known to a person of ordinary skill in the art, is a water-soluble cyclic, oligosaccharide produced when starch degrades. Its cylindrical structure, having a hydrophobic interior and hydrophilic exterior, binds or chelates substances. Applicants' specification discloses the following effects of cyclodextrin (p. 22, quoted above):

> Large fluorescence enhancement of dyes have been observed under the condition where the dye is encapsulated in, i.e. forms an inclusion complex with, cyclodextrins (W.R. Bergmark et al., Dramatic fluorescence effects for coumarin laser dyes coincluded with organic solvents in cyclodextrins. *J. Phys. Chem.*, 1990, 94, 5020[[8]]-5022).

Because Licha teaches that water solubility, toxicity, and stability are the problems that its invention is addressing (cols. 3 lines 35-44 and 14 lines 45-52), and because Licha in fact teaches away from the need to enhance fluorescence, as Applicants have previously analyzed, a person skilled in the art, based on Licha, would not even consider cyclodextrin to achieve enhanced fluorescence.

Claims 32-35 are rejected under 35 U.S.C. §103(a) as obvious over Rajagopalan U.S. Patent No. 6,423,547.

Applicants respectfully disagree with the Examiner's substantive basis for rejection. Applicants attach the required showing under 37 C.F.R. §1.132 that the invention disclosed but not claimed in the '547 patent was derived from the inventor of the present application and thus is not an invention "by another".

Claims 32-35 are rejected under 35 U.S.C. §103(a) as obvious over Miwa et al U.S. Patent No. 7,488,468.

The Examiner states

> Miwa et al disclose near infrared fluorescent contrast agents ....The contrast agent comprises a cyanine dye (column 2, lines 13-40)...that is suspended or dissolved in a solvent such as injectable distilled water. Additional additives such as cyclodextrin may be added to adjust osmotic pressure and improve stability and solubility (column 65, lines 7-23). Thus, while Miwa et al does not specifically state that their composition is useful in a method of enhancing fluorescence, it would have been obvious to one skilled in the art at the time of the invention to generate a composition comprising a cyanine dye in combination with a cyclodextrin solution useful in a method of enhancing fluorescence for the reasons set forth below. First, both Applicant and the prior art disclose a cyanine dye that may be used in combination with cyclodextrin. Secondly, both the instant invention and that of the prior art are directed to contrast agents that are useful in a method of fluorescence imaging. Third, while the prior art does not specifically state that the purpose of using cyclodextrin (to enhance fluorescence) is the same as Applicant, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the difference would otherwise be obvious. In regards to determining the concentration of cyclodextrin necessary to yield 'enhanced' results, the quantity of experimentation needed to be performed by one skilled in the art is reasonable (merely routine). A skilled artisan would be motivated to alter the concentration of the carrier solution to obtain maximum results. Thus, both Applicant and the prior art disclose overlapping subject matter [Action p. 11-12, internal citations omitted].

Applicants respectfully disagree. A skilled artisan would not "be motivated to alter the concentration of the carrier solution to obtain maximum results", at least because the skilled person reading Miwa would not get any teaching that cyclodextrin can be used as one example of a biocompatible organic solvent, at a concentration ranging from about 1% to about 50%, to enhance fluorescence of the cyanine or indocyanine dye.

Applicants note their election of the specie of DMSO, not cyclodextrin, as the biocompatible organic solvent.

Applicants restate their facts regarding cyclodextrin: as known to a person of ordinary skill in the art, it is a water-soluble cyclic, oligosaccharide produced when starch degrades. Its cylindrical structure, having a hydrophobic interior and hydrophilic exterior, binds or chelates substances.

In contrast, Miwa relies on cyclodextrin's known function as a carrier to adjust osmotic pressure and to improve stability and solubility.

> Where necessary, pharmacologically acceptable additive such as carrier, excipient and the like may be added. These additives contain substances such as pharmacologically acceptable electrolyte, buffer, detergent and a substance for adjusting osmotic pressure and improving stability and solubility (e.g., cyclodextrin, liposome and the like) (col. 65 lines 17-23).

Miwa's teachings are akin to Licha's teachings, analyzed above: dyes that overcome prior art problems of toxicity, water solubility, chemical, photophysical, and metabolic stability by adding a hydrophilic group that improves water solubility. In contrast, Applicants' claims require adding 1%

to 50% of a biocompatible organic solvent to a dye composition in order to enhance in vivo fluorescence of the dye.

Additionally, because Miwa teaches that its "inventive contrast agent is superior in water solubility and low toxic [*sic*], a person skilled in the art, based on Miwa would not be motivated to alter the concentration of the carrier solution to maximize results, as the Examiner states. There would be no need to enhance fluorescence, because Miwa's invention already provides "infrared fluorescence [that] is superior in transmission through biological tissues" (Abstract, emphasis added).

For at least these reasons, Applicants respectfully assert that claims 32-35 are not obvious, and request the rejection be withdrawn.

CLAIM REJECTIONS UNDER 35 U.S.C. §112

Claims 32-35 and 45-51 are rejected under 35 U.S.C. §112 ¶1 as not described.

The Examiner states

> The instant application does not sufficiently describe the invention as it relates to the types of cyanine and indocyanine dyes that are compatible with the instant invention.

As Applicants themselves have elucidated in their February 26, 2009 Amendment, the term "cyanine dye" encompasses all specific examples in the group.

> Cyanine dye. One of a series of dyes consisting of two heterocyclic groups (usually quinoline nuclei) connected by a chain of conjugated double bonds containing an odd number of carbon atoms. Example: cyanine blue $C_2H_4NC_9H_6$:$CHC_9H_6NC_2H_2$. They include the isocyanines, merocyanines, cryptocyanines, and dicyanines. (Hawley's Condensed Chemical Dictionary, 14th Ed., John Wiley & Sons, Inc. New York 2001), emphasis added).

In further support of Applicants' position that claims 32-35 are sufficiently described, they attach as part of this Amendment a Declaration under 37 C.F.R. §1.132 with an explanation of why the rejections are improper. The Examiner states:

> In addition, according to Licha et al (US Patent No. 6,083,485), the classes of cyanine dyes are structurally different. For example, in column 5, line 1, Licha et al disclose a general formula for a cyanine dye. In columns 6-7, bridging paragraph, Licha disclose a general formula for merocyanine dyes. It should be noted that the structure of the merocyanine dyes are different from those having the general cyanine dye formula. Other structurally different cyanine dyes include those found in columns 10-11, bridging paragraph (Licha et al) that differ in how the variable Q is defined.

The Examiner's statement is not entirely complete. Licha's col. 5 line 1 structure is one of a general formula, in accord with the dictionary definition of a cyanine dye. Cyanine dyes are any molecules with a charged nitrogen on the left side of the molecule, connected to a polymethine group. The Licha structures to which the Examiner refers are examples of specific types of cyanine dyes; although they have different structures, they each contain the core cyanine

structure. The Declaration explains the chemical nomenclature and structures in detail, and explains how each compound is properly a cyanine dye.

In the alternative and only to advance prosecution, should the Examiner disagree with Applicants' position, new claims 53-57 clarify that the dye is one that contains a hydrophobic core that form aggregates in aqueous media, supported in the specification at least at p. 22:

> It is known that cyanine dyes generally form aggregates in aqueous media, leading to fluorescence quenching. Where the presence of a hydrophobic core in the dyes leads to fluorescence quenching, the addition of a biocompatible organic solvent, such as 1-50% dimethylsulfoxide (DMSO) for example, restored fluorescence by preventing aggregation and allowed *in vivo* organ visualization.

The clarification addresses the Examiner's concern:

> While compliance with the written description requirements must be determined on a case-by-case basis, the real issue here is simply whether an adequate description is necessary to practice an invention described only in terms of its function and/or based on a disclosure wherein a description of the components necessary in order for the invention to function are lacking.

because all cyanine and indocyanine dyes that contain a hydrophobic core, and that form aggregates in aqueous media, are compatible with the instant invention.

> Claims 32-35 and 45-51 are rejected under 35 U.S.C. §112 ¶2 as indefinite.
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> The Examiner states
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> The claims as written are ambiguous because it is unclear what cyanine and indocyanine dyes Applicant is claiming that are compatible with the instant invention.

Applicants respectfully disagree and incorporate their arguments above as detailed in the attached Declaration under 37 C.F.R. §1.132 explaining why the claims are not ambiguous, and why a person skilled in this art would know what cyanine and indocyanine dyes Applicants are claiming that are compatible with claims 32-35.

Applicants thus assert the rejections under 35 U.S.C. §112 ¶¶1 and 2 are overcome and respectfully request their withdrawal.

CONCLUSION

Applicants believe the application is in complete condition for allowance with no fees due. If fees are deemed necessary, the Office is authorized to charge them to Deposit Account No. 20-0809.

The Examiner is invited to contact Applicants' undersigned representative with questions.

Respectfully submitted,
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